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TECHNICAL NOTE

Aluminum leakage from REDY sorbent cartridge

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Although hemodialysis (HD) is able to keep patients with endstage renal disease (ESRD) alive, it does not completely reverse many of the sequellae of chronic renal failure. Hemofiltration (HF) based on convective transport principles similar to that of the natural kidney has been shown to have important advantages over HD. Studies have demonstrated that HF can result in: stabilization of blood pressure during treatment [1]; better control of hypertension between treatments [2]; improvement in uremic symptomatology [3]; improvement in uremic neuropathy [4]. One important drawback to HF as practiced today is the need to replace the large quantities of ultrafiltrate produced by an equal amount of sterile, pyrogen-free electrolyte solution. This procedure is costly and requires precise monitoring to avoid surfeits and deficits. To overcome this major drawback of HF, we examined a method of recycling ultrafiltrate by cleansing it with a sorbent system.

This sorbent recycling of ultrafiltrate (SRUF) system utilizes an Amicon Diafilter (Amicon Corporation, Lexington, Massachusetts) as the ultrafilter and a REDY sorbent cartridge (RSC) (Organon Teknika Corporation, Oklahoma City, Oklahoma) as the sorbent system. The standard (3150) RSC which was to be used in our SRUF system has been in use since 1974 to regenerate dialysis fluid. It is composed of the following layers from bottom to top (the direction of fluid flow): *(1)* purification layer consisting of activated carbon, alumina (aluminum oxide) and hydrated zirconium oxide in the chloride form to remove heavy metals, bleach, formaldehyde, and other trace materials which could adversely effect the urease layer; *(2)* urease stabilized with alumina to degrade urea by converting it into ammonium carbonate; *(3)* zirconium phosphate (ZP), a cation exchanger present in both the sodium (Na-ZP) and hydrogen (H-ZP) forms, which exchanges these cations for ammonium produced from urea breakdown and also for calcium, magnesium, and potassium present in the ultrafiltrate; *(4)* hydrated zirconium oxide in the acetate form (H-ZO-AC) mixed with alumina to remove phosphate and fluoride; *(5)* activated carbon which removes creatinine and other organic compounds. The alumina in the RSC was first thought to be inert. However, aluminum has been incriminated in the development of dialysis osteomalacia and dialysis dementia after prolonged hemodialysis treatment with the RSC [5].

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Unlike HD where there is a membrane separating the RSC from the circulation, the SRUF procedure utilizes the RSC to cleanse ultrafiltrate which is then returned directly to the blood. Thus, any aluminum leaking from the RSC would have direct access to the blood. Early work from Shaldon et al [6] indicated that the RSC, when used to cleanse ultrafiltrate, leaks aluminum in significant amounts but that this problem could be eliminated by passing the post-RSC fluid through an Amicon Diafilter to remove particulate matter. Later work from this same group indicated that patients treated chronically with a system in which an RSC was used to cleanse ultrafiltrate developed severe bone disease and elevated blood aluminum levels despite passage of ultrafiltrate through a second sterilizing Amicon Diafilter [7].

Therefore, prior to utilizing the SRUF system clinically, we examined the RSC for aluminum leakage in vitro and in vivo in dogs. Our results indicate that aluminum leaks from the standard RSC in amounts that could be toxic and that it is not removed by an Amicon Diafilter. The problem was corrected, however, by producing a modified RSC in which the alumina filler was removed. The modified RSC produced by Organon Teknika and now marketed as the 3160 cartridge (with United States Food and Drug Administration approval) is composed of the following layers: *(1)* purification layer made of carbon and hydrated zirconium oxide in the chloride form but without alumina; *(2)* urease stabilized with alumina; *(3)* ZP in both the Na-ZP and H-ZP forms; *(4)* H-ZO-AC without alumina; *(5)* activated carbon. All layers in the 3160 RSC have the same purpose as in the 3150. The volume formally occupied by the alumina has been filled by a polystyrene spacer.

Methods. For all protocols the 3150 (standard) and 3160 (modified) RSC were used. Each RSC was prerinsed twice. The first prerinse was used to titrate the H-ZP/Na-ZP buffer pair toward the basic side and consisted of 4.5 liters of 190 mM sodium bicarbonate which was pumped through the RSC at a rate of 100 ml/min until 3 liters were collected in a graduated cylinder (the dead space volume of the RSC is 1.5 liters). The second prerinse was utilized so that the initial sodium concentration post-RSC at the start of a study would be uniform and at a physiologic level and consisted of 3 liters of 120 mM sodium chloride pumped through the RSC in the same manner as the first prerinse.

Control studies. To determine whether or not differences in the composition between artificial and uremic dog ultrafiltrate would lead to alterations in the measurement of aluminum, we sent samples of both ultrafiltrates for aluminum determination

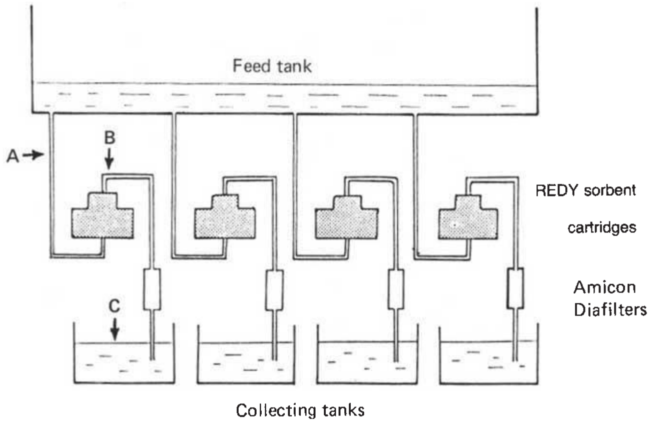

Fig. 1. *Schematic diagram of the apparatus used for in vitro aluminum leakage studies.* Samples were taken for aluminum analysis from the following sites: **A**, the feed tank; **B**, distal to the RSC; **C**, collecting tanks distal to the Amicon Diafilters.

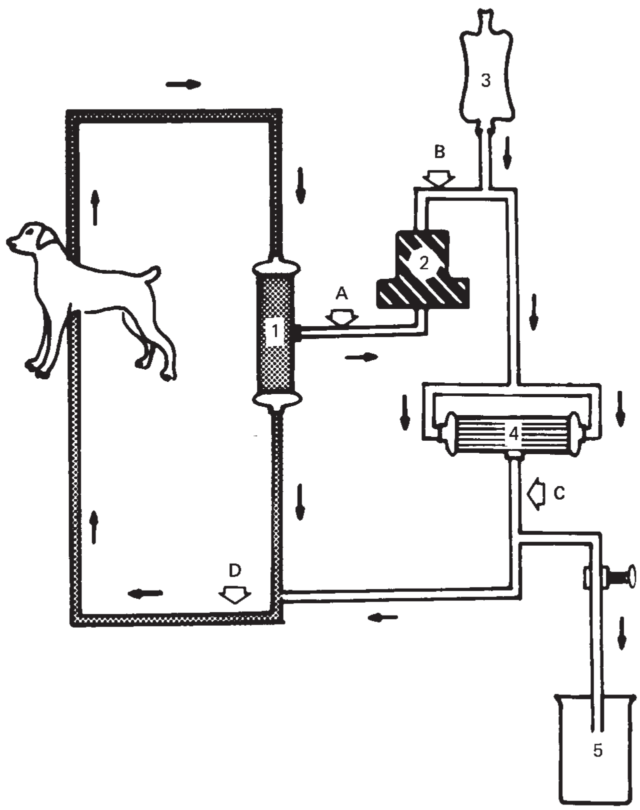

Fig. 2. *Schematic diagram of the SRUF system used for in vivo aluminum leakage studies.* Samples were taken for aluminum analysis from the following sites: **A**, ultrafiltrate post-Amicon Diafilter; **B**, ultrafiltrate post-RSC; **C**, ultrafiltrate poststerilizing Amicon Diafilter; **D**, blood post-Amicon Diafilter combined with cleansed ultrafiltrate prior to return to the animal. The numbers are: 1, Amicon Diafilter (0.5 m^2); 2, REDY sorbent cartridge; 3, infusate; 4, sterilizing Amicon (0.5 m^2); 5, fluid removal tank.

by flameless atomic absorption (courtesy of Dr. A. Alfrey, University of Colorado) [8, 9]. These and all other samples were stored and shipped in aluminum-free plastic containers and analyzed in an identical manner. Uremic dog ultrafiltrate was a pooled sample (six animals) postmodified RSC at 180 min from site **C** (Fig. 2). At the laboratory the samples were subdivided into 5 aliquots to which one of five aluminum standard solutions was added. The standards contained aluminum at the concentrations listed in Table 1. Controls, consisting of deionized water plus the same aluminum standards, were analyzed together with the ultrafiltrate samples.

Table 1. Comparison of aluminum determinations in deionized water, artificial, and uremic ultrafiltrate (μg/liter)

Aluminum standard	Deionized water plus standard	Artificial ultrafiltrate plus standard	Uremic dog ultrafiltrate plus standard[a]
0	0	0	4
13	13	14	17 (13)
26	27	28	28 (24)
52	57	59	68 (64)
104	113	113	117 (113)

[a] Numbers shown in parentheses represent values corrected by subtracting the initial aluminum concentration.

Table 2. Aluminum determinations (μg/liter ± SEM) during SRUF utilizing the standard RSC[a]

Time, *min*	Site **A**	Site **B**	Site **C**
In vitro (N = 4)			
0	14 ± 8	94 ± 33[b]	81 ± 37[b]
60	4 ± 1	30 ± 7[b]	19 ± 6[b]
120	3 ± 1	41 ± 9[b]	30 ± 5[b]
180	5 ± 1	30 ± 12[b]	37 ± 3[b]
In vivo (N = 13)			
0	11 ± 5	28 ± 6	26 ± 7
180	33 ± 13	231 ± 106[b]	192 ± 68[b]

Abbreviations: RSC, REDY sorbent cartridge; SRUF, sorbent recycling of ultrafiltrate.
[a] For location of in vitro sites see Figure 1; for location of in vivo sites see Figure 2.
[b] $P < 0.005$ vs. **A**.

In vitro studies. Four standard and four modified RSCs were studied simultaneously using the in vitro system depicted schematically in Figure 1. Each of the prerinsed RSCs was perfused with 25 liters of an artificial ultrafiltrate containing Na 150, Cl 137, K 7, HCO_3 20, and urea 18 mM/liter pumped from the feed tank at a rate of 120 ml/min. Samples were taken at times and sites as indicated in Tables 2 and 3 and Figure 1 for aluminum analysis as described above. Site **A** is the feed tank, site **B** is post-RSC and site **C** is the collecting tank distal to the Amicon Diafilter used to remove particulate matter.

In vivo studies. Figure 2 depicts schematically the SRUF system used for these studies. Twenty dogs were made uremic by bilateral ureteral ligation 2 days prior to the experiment which consisted of 180 min of SRUF at an UF flow rate of 50 ml/min with the RSC prerinsed as in the in vitro studies. The only difference between in vitro and in vivo studies was that the SRUF system (blood and ultrafiltrate lines, Amicon Diafilters and degassing filters) were rinsed with saline and air purged from the system. Calcium and magnesium are removed from the

Table 3. Aluminum determinations (μg/liter ± SEM) during SRUF utilizing the modified RSC[a]

In vitro (N = 4)				
Time, *min*	Site **A**	Site **B**	Site **C**	
0	5 ± 0	4 ± 1	2 ± 1	
60	5 ± 0	4 ± 1	3 ± 1	
180	5 ± 0	6 ± 3	3 ± 1	
In vivo (N = 7)				
Time, *min*	Arterial plasma	Site **A**	Site **B**	Site **D**
0	3.0 ± 0.7	3.0 ± 1.2	3.5 ± 1.0	3.0 ± 0.6
90	2.7 ± 0.6	2.8 ± 0.9	2.0 ± 0.0	3.8 ± 1.7
120	4.1 ± 1.1	4.5 ± 1.7	2.4 ± 0.5	4.0 ± 1.2
180	6.9 ± 1.8	2.0 ± 0.0	8.0 ± 2.4	5.3 ± 1.3

[a] For location of in vitro sites see Figure 1; for location of in vivo sites see Figure 2. Abbreviations are in Table 2.

ultrafiltrate by the RSC and were replaced with 3 mEq/liter Ca and 1 mEq/liter Mg at a point distal to the RSC (see 3 in Fig. 2). Samples for aluminum analysis were taken at the times and sites indicated in Tables 2 and 3 and Figure 2. Site **A** (ultrafiltrate post-Amicon Diafilter), site **B** (ultrafiltrate post-RSC), site **C** (ultrafiltrate poststerilizing Amicon which is used to remove particulate matter) and site **D** (blood post-Amicon Diafilter combined with cleansed ultrafiltrate prior to return to the animal). Site **D**, like site **C**, will reflect aluminum leakage from the RSC. All results are expressed as the mean ± SD. Statistical analysis was performed by Student's t test or analysis of variance where appropriate.

Results. Table 1 summarizes the results of the control studies. It can be seen that deionized water, artificial ultrafiltrate which was made with tap water and the uremic dog ultrafiltrate show similar concentrations of aluminum after the addition of the aluminum-containing standard solutions.

Table 2 summarizes the results of the in vivo and in vitro studies with the standard RSC. Aluminum levels did not vary significantly with time in the in vitro studies but were significantly higher at **B** and **C** (both sites distal to the RSC) compared to **A** (pre-RSC). There were no significant changes in aluminum levels when the fluid was passed through an Amicon Diafilter (**B** vs. **C**). Aluminum concentration at the start of the in vivo SRUF procedure (zero time) was similar at all sites. At 180 min (the end of the procedure) aluminum levels at **B** and **C** had increased markedly. There were no significant changes in aluminum levels when the ultrafiltrate was passed through the sterilizing Amicon Diafilter (**C** vs. **B**).

The results of in vivo and in vitro tests with the modified RSC are summarized in Table 3. Aluminum did not leak from this RSC in physiologically significant quantities. At all times in the in vitro studies (0, 60, and 180 min) aluminum levels were at the lower limits of the sensitivity of the test. Aluminum levels in the in vivo studies were measured in arterial plasma, sites **A**, **B**, and **D** at 0, 90, 120, and 180 min. At no time were the mean aluminum levels greater than 10 μg/liter, the permissible limit of aluminum concentration for water used to prepare dialysate [10].

Discussion. The data demonstrate that the standard RSC leaks toxic amounts of aluminum when used as a sorbent cleanser in an ultrafiltration system designed to recycle ultrafiltrate rather than discard it. On the basis of this finding, a modified RSC has been designed in which aluminum was removed from points distal to the urease layer. When tested in the same systems in which the standard RSC leaked large amounts of aluminum, aluminum levels remained at the lower limit of detection making this RSC sorbent system acceptable for application to our SRUF system and more acceptable for use in cleansing dialysate in hemodialysis as well.

An interesting observation in the present experiments is that the aluminum leakage was significantly greater when the standard RSC was exposed to uremic dog plasma than when exposed to an artificial ultrafiltrate (Table 2). The similar Al levels in deionized water, artificial and uremic dog ultrafiltrate in the control studies suggest that the difference between artificial and uremic dog ultrafiltrate aluminum concentration is not an artifact of analysis. It is possible that the uremic dog ultrafiltrate compromised the integrity of the RSC leading to its dissolution. The particles of aluminum (as alumina) released could then have been responsible for the elevated aluminum levels. This possibility is unlikely because we have inserted a second (sterilizing) Amicon distal to the RSC which traps any particles released from the RSC. We have examined the post-RSC, post-Amicon uremic dog ultrafiltrate under the microscope on numerous occasions and at no time have particles been seen distal to the sterilizing Amicon (Shapiro, Schilb, Waltrous, Levy, and Porush, personal observations). Another possible explanation for the difference is that uremic dog ultrafiltrate may result in greater changes in pH than artificial ultrafiltrate leading to solubilization of the alumina. Although we cannot measure the internal pH of the RSC there was no difference in the post-RSC pH between artificial and uremic dog ultrafiltrate (Shapiro, Schilb, Waltrous, Levy, and Porush, personal observations). Finally, it is possible that some component or property of uremic dog ultrafiltrate which passes through the Amicon Diafilters promotes solubilization of the alumina in the RSC. This possibility appears most likely but was not addressed in the present experiments.

Acknowledgments

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